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Application of Salivary Biomarkers in Malignant Transformation of Oral Potentially Malignant Disorders

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Abstract: *Oral cancer is a major global health challenge, with its incidence and mortality rates rising over recent decades. Early detection and accurate diagnosis are crucial. Oral potentially malignant disorders (OPMDs) are conditions that carry a risk of evolving into squamous cell carcinoma (SCC). Detecting the malignant transformation of OPMDs early is critical for effective prevention and management of SCC. Salivary biomarkers offer a non-invasive and convenient method for clinical diagnosis and prognosis of oral and even systemic diseases. This review explores various salivary biomarkers that differ between OPMDs and SCC, providing a foundation for future progress in the early diagnosis, treatment, and monitoring of cancer.*

Keywords: *OMPDs; MT; Saliva Biomarkers; OSCC*

1. Introduction

With the increasing prevalence of unhealthy lifestyles, the number of risk factors for oral cancer is increasing. Worldwide, the incidence of oral squamous cell carcinoma (OSCC) has been gradually increasing. Thus, early detection, prevention and treatment of oral cancer have become especially important. Oral potentially malignant disorders (OPMDs) refer to the collective term for lesions or conditions occurring in the oral mucosa that possess latent potential for malignancy. These conditions serve as precursors that could potentially develop into oral cancer, with the probability of malignant transformation varying significantly across different sites [1]. Prior to 2005, the nomenclature for these diseases or conditions was not uniform. Following a workshop held in the UK by the World Health Organization's (WHO) Collaborating Centre for Oral Cancer, terms including "precancerous lesion," "preepithelial lesion," "precancerous condition," "precancer stage," and "intraepithelial lesion" were consolidated under the new term "Oral Potentially Malignant Disorders" (OPMDs) [2]. At the 2020 OPMD workshop, a group of specialists approved the continuation of the current OPMD terminology to refer to oral mucosal disorders, signifying an elevated risk of cancer. The current list of lesions supported by adequate evidence includes oral leukoplakia, oral erythroplakia, proliferative venous leukoplakia, oral submucous fibrosis, oral lichen planus, keratosis/acrocheilon, palatal lesions in reverse smokers, oral lupus erythematosus, dyskeratosis congenita, oral lichenoid lesions, and chronic graft-versus-host disease [3].

Currently, screening for malignant transformation (MT) of OPMDs relies primarily on routine oral examination (COE), with definitive diagnosis confirmed by gold standard biopsy and histological examination. However, this examination method has limitations. First, COE requires experienced and well-trained clinicians who can still be subjective in their assessments; second, subtle or invisible clinical changes resulting from early malignant transformation can easily be overlooked; furthermore, biopsy and histopathological examination are invasive and cannot facilitate real-time assessment. In recent years, researchers have explored the potential of human saliva as an important diagnostic fluid. Saliva, which is rich in proteins, offers a simple, inexpensive, safe, and noninvasive approach for disease detection, with high potential for revolutionary diagnostics. Salivary biomarkers can be used for health monitoring and disease surveillance, and biomarkers showing significant differences between OSCC and OPMD could serve as references for further screening of already transformed OMPD. This article summarizes biomarkers that can confirm the carcinogenic transformation of potentially malignant oral disorders, providing insights for early clinical diagnosis and prevention.

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2. Salivary Biomarkers Distinguishing between OPMD and SCC

2.1 Oral leukoplakia

Oral leukoplakia presents as a chronic inflammatory response secondary to smoking, wherein various inflammatory mediators cause cellular damage or death, concurrently inducing free radical production and leading to an imbalance in the antioxidant defense system. Babiuch K et al. [4] conducted activity assays on total antioxidant capacity and related derivatives in saliva and reported that superoxide dismutase (SOD) activity, which is dependent on metal ions, was markedly greater in the OSCC group compared to the OL group and the healthy controls. This is due to SOD being one of the key enzymatic components of the antioxidant defense system. Cytokines, which are small protein molecules produced and released by immune or nonimmune cells in response to stimulation, are closely linked to the inflammatory cells that play a role in tumor initiation and development. These cytokines promote inflammation by facilitating the recruitment of macrophages and neutrophils. Among the proinflammatory cytokines, those dependent on NF-kB, especially interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α), are crucial in the malignant transformation of the oral mucosa and contribute significantly to the development of OPMDs to OSCC. Babiuch K et al. [5] demonstrated through immunohistochemical analysis that the levels of IL-8 in oral squamous cell carcinoma patients were greater than those in dysplastic OPMD patients; they also reported that the expression level of IL-6 increased in the leukoplakia group in correlation with the severity of dysplasia. In a study by Oshin M et al. [6], the levels of IL-6 in both the saliva and serum of oral squamous cell carcinoma patients were significantly greater than those in oral leukoplakia patients and healthy controls, with statistically significant differences. Of the cytokines evaluated, IL-8 appears to be the key biomarker associated with the MT of the oral mucosa. According to Sridharan G et al. [7] , salivary levels of IL-6, 8 and TNF-α, the long noncoding RNA (lncRNA) HCC-1, and PF-4 could serve as distinguishing markers among patients with OSCC, those with OL, and healthy individuals. Specifically, IL-6 and TNF-α might reflect the advancement of OSCC, especially in patients with cervical lymph node metastasis. Sridharan G et al. [8] reported that, compared with oral leukoplakia, sphingosine-1-phosphate (S1P), galactosylceramide, pseudouridine, 4-nitroquinoline-1-oxide, ubiquinone, inositol 1 and 3,4-triphosphate (IP3R) were significantly upregulated in OSCC, whereas p-alpha-chlorophenylalanine, l-alpha-isoleucine, and 4-alpha-fumaroylacetoacetate were significantly downregulated. Among these, S1P is also associated with survival rates, and chemical inhibitors targeting IP3R are considered potential treatments for advanced metastatic cancer; additionally, decreased levels of ubiquinone, one of the most important lipophilic antioxidants, are correlated with poor cancer prognosis.

The abnormal release and activation of protein markers can lead to pathological alterations in cells, tissues, and organs, particularly during the processes of cancer development and metastasis. Kang Y et al. [9] measured the levels of two proteases: salivary kallikrein 5 (KLK 5) and urokinase-type plasminogen activator (uPA) via ELISA and reported that their levels could be used to discriminate between the OSCC and OL groups. KLK5 played a supplementary role in identification but was insufficient on its own; the optimal diagnostic cutoff values for KLK5 in the healthy, OL, and OSCC groups were 5.97 pg/mL, 6.03 pg/mL, and 9.45 pg/mL, respectively, whereas those for uPA were 17.19 pg/mL, 17.26 pg/mL, and 20.96 pg/mL, respectively. Jointly, they can distinguish high-grade carcinomas from low-grade squamous cell carcinomas. In their study on saliva metabolomics in OL and OSCC, Wei J et al. [10] found that the concentrations of gamma-aminobutyric acid (GABA), phenylalanine, and valine were notably reduced in the OSCC group when compared to both the OL and healthy control groups. Conversely, the concentrations of eicosanoic acid and lactate were markedly greater in the OSCC group than in the OLK and healthy groups. The authors suggested that lactate, valine, and phenylalanine serve as the best predictive factors for discriminating OSCC from OLK. Prior research has demonstrated that high expression of synuclein-gamma (SNCG) can significantly stimulate cell proliferation, invasion, and differentiation. In OSCC, the levels of SNCG are significantly higher in SCC tissues compared to adjacent normal tissues, where its expression is diminished. Its expression in OSCC is significantly correlated with the degree of differentiation [11]. Wei et al. [12] reported that, compared with that in leukoplakia patients, plectin expression in cancer patients was increased by up to 1.5-fold, and lactate dehydrogenase A (LDHA) expression was altered by 1.4-fold.

Multiple studies have shown the practicality of utilizing saliva-based miRNAs and long noncoding RNAs (lncRNAs) as promising biomarkers for diagnosing metastasis in OSCC patients. Michailidou E et al. [13] confirmed that the transcripts of miRNAs for spermine/spermidine N1-acetyltransferase 1

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(SAT), ornithine decarboxylase antizyme 1 (OAZ), interleukin-1 beta (IL-1B), and interleukin-8 (IL-8) can be used for early detection of OSCC, distinguishing it from oral leukoplakia with dysplasia, providing predictive probabilities of up to 80%, but cannot distinguish leukoplakia from patients who have undergone oral mucosal dysplasia. Uma Maheswari et al. [14] reported significantly elevated levels of miRNA-21, 31 in severe dysplasia, with miRNA-21 being associated with poor prognostic outcomes in tongue squamous cell carcinoma, potentially serving as an early diagnostic biomarker for cancer development and exhibiting greater potential than miRNA-31. miRNA-31 promotes cell proliferation by silencing negative regulators of cancer pathways. Zhao et al. [15] reported that hsa circ0001971 in circular RNAs could discriminate between OSCC and OL; high expression levels of hsa circ0001874 correlated with TNM stage and tumor grade, whereas the expression levels of hsa circ0001971 were linked solely to TNM stage. Shah et al. [16] reported a significant increase in the expression of the cell-free nucleic acids CD44v6 and CD44v10 in OSCC, whereas SYNE1 and miRNA34a presented significantly decreased expression. Patients with moderate differentiation presented higher CD44v10 expression levels and markedly lower miRNA34a expression than well-differentiated patients did. The expression levels of CD44v6, CD44v10, and miRNA34a were also significantly associated with lymph node metastasis and recurrence in patients.

In the category of low-molecular-weight organic compounds used as biomarkers, Tantray et al. [17] reported upregulated salivary metabolites such as decanedioic acid, 2-methylnonacosane and metoprolol, among others, which may hold clinical utility in discriminating between oral leukoplakia and OSCC.

Microbial biomarkers related to leukoplakia and OSCC also show some utility. Hashimoto et al. [18], through quantitative insights into microbial ecology, reported that the relative abundances of Bacteroidetes, Streptococcus, and Solobacterium were significantly different between the OSCC group and the OL group, with higher levels of Bacteroidetes and Solobacterium and significantly lower levels of Streptococcus in OSCC.

2.2 Proliferative venous leukoplakia (PVL)

PVL, a variant of OL that presents with a verruciform appearance and often resists treatment, later progressing into verrucous carcinoma or invasive SCC with a high recurrence rate. Both to the naked eye and under the microscope, the early manifestations of PVL can be challenging to distinguish from other forms of leukoplakia or lichenoid lesions, necessitating diagnosis through observing the duration and clinicopathological evolution of the lesion.

Koh et al. [19] demonstrated that Toll-like receptor (TLR) 2 is upregulated in both premalignant lesions and malignant cells, is capable of activating oncogenic pathways, and contributes to the initial phases of squamous cell carcinoma progression. It functions primarily by reinforcing the tight junctions between the barrier and keratinocytes, is diffusely expressed throughout the epithelium, and can distinguish the PVL from other oral premalignant lesions.

Gouvêa et al. [20] reported that the genes Mcm-2 and Mcm-5 were highly expressed in patients with mild to moderate dysplasia, particularly in OSCC patients, aiding in predicting the malignant transformation of PVL. P53 and Ki-67 were weakly positive in the mildly to moderately dysplastic epithelial samples but strongly positive in the OSCC samples. The immunopositivity of these two proteins was associated with increasing grades of epithelial dysplasia, with higher immunopositivity indicating poorer prognosis. Furthermore, the research team confirmed that increases in Mcm-2 and Geminin correlate with the progression from normal mucosa to dysplastic epithelium to OSCC, with Mcm-2 showing greater expression than Ki-67 and Geminin. They also reported anomalous DNA content, which contrasts with findings in other premalignant conditions, and aneuploidy (abnormal DNA content) was more likely to progress to malignancy regardless of the grade of epithelial dysplasia [21]. Rintala et al. [22] performed a meta-analysis on the previously mentioned markers, including Ki-67, P53, HPV, and aneuploidy, and determined that aneuploidy acts as an indicator of a heightened risk for MT progression, regardless of the presence of epithelial dysplasia.

Numerous researchers have investigated aberrant gene methylation between PVL and OSCC, and Herreros-Pomares et al. [23] identified five hypermethylated and 21 hypomethylated genes. As shown below, DKK4 and SMPD3 correlate with OSCC tumor grade, CLCN1 predicts OSCC survival, NKX2-3 is associated with prognosis, and BARX2 expression inhibits OSCC cell proliferation. Kresty et al. [24] evaluated the homozygous deletion, heterozygous deletion, and mutation events of the cell cycle regulatory genes p16INK4a and p14ARF, which are prevalent in PVL and ultimately result in

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total deletion of the INK4a/ARF locus in terminal-stage oral cancer.

2.3 Oral Erythroplakia (OE)

Owing to the rarity of OE, research on salivary biomarkers for its metastasis is scarce. In most cases, studies on OL include a small proportion of OE, which is typically researched alongside OL. The diameter of the lesion is generally less than 1.5 cm. Histopathologically, the lesion often shows moderate to severe dysplasia. The malignant transformation rate of leukoplakia reportedly ranges from 0.13% to 19.8%, whereas that of erythroplakia is significantly greater, exceeding 50%.

Goyal G et al. [25] conducted the first study to investigate the changes in alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels from benign oral stages to precancerous stages and further to malignant cancer, refining their analysis to atypical hyperplasia of different histological grades and concluding that ALP and LDH can serve as sensitive indicators for detecting precancerous lesions and atypical hyperplasia. Sridharan G et al. [26] investigated differential protein expression in OE and cancer phenotypes and reported that LDH A chain, ALDH 2, peroxiredoxin 1 (PRDX 1) and so on , the concentrations of LDHA in cancer patients was nearly 1.9 times greater than in OE patients; they also reported lower HSPA 1B expression in cancer patients than in OE patients and lower saliva thioredoxin (TXN) levels in patients with ulcerative SCC.

2.4 Oral submucous fibrosis (OSFF)

OSMF, often caused by betel nut chewing, is characterized by its idiosyncratic features and various immunological alterations, leading many researchers to view it as an autoimmune disorder. The quantification of immunoglobulins is the most commonly performed test for humoral immunity screening. Typically, testing for the two major categories of immunoglobulins (immunoglobulin G [IgG] and immunoglobulin A [IgA]) is sufficient, as there is no evidence suggesting that deficiencies in other classes might produce pathological consequences.

Meera S et al. [27] investigated the plasma and salivary 8-iso-prostaglandin levels in patients with OSCC, patients with OSMF, and healthy controls and reported significantly distinct levels of 8-iso-prostaglandin in the saliva, with a progressive increase. Mantri T et al. [28] reported highly significant differences in the mean values of LDH among a healthy control group, an oral cancer group, an OSMF group, and habitual tobacco chewers. Moorthy A et al. [29] stated that the epidermal growth factor receptor (EGFR) shows elevated levels in OSCC, with 18-fold greater expression in OSCC patients than in healthy controls and 3-fold greater expression in OSMF patients. Sabarathinam et al. [30]indicated that the concentrations of the receptor for advanced glycation end products (RAGE) were higher in individuals with OSMF in comparison to those with OSCC. Punyani S R et al. [31] reported that salivary IL-8 levels in OSCC patients were significantly higher than those in the precancerous OSMF group ($p < 0.0001$) as well as the healthy control group. SHAFIQ N et al. [32] reported that hypoxia inducible factor-1 (HIF-1α) may be an effective factor in the MT of oral submucous fibrosis, potentially playing a crucial role in fibrosis-induced carcinogenesis and possibly even serving as a cause of fibrosis.

2.5 Oral lichen planus (OLP)

OLP typically persists for many years with a low likelihood of spontaneous resolution; it may temporarily disappear following treatment. It often cooccurs with cutaneous and genital lesions, and while the etiology remains unclear, it is largely attributed to oxidative stress-induced pathology. Its mechanism of malignant transformation has yet to be elucidated, but it is widely recognized as an ideal model for studying inflammation-induced carcinogenesis. Ezelj-Ribaric et al. [33] reported that the presence of TNF-alpha correlates positively with the clinical form of OLP, which is notably greater in patients with erosive or atrophic variants of the disease than in those with the reticular type. The persistent or long-term high levels of TNF-alpha in saliva may contribute to signaling the MT of OLP lesions. Mansourian et al. [34] reported that ALDH (aldehyde dehydrogenase) functions similarly to a common marker for both normal and cancer stem cells by mitigating the oxidative stress caused by aldehydes. This is the first report of a significant increase in ALDH1&2 in OLP (oral lichen planus), which is notably more pronounced in erosive OLP than in mild and nondysplastic OL. Determining whether this expression pattern indicates an early epithelial "CSC" phenotype in OLP or if ALDH1 and ALDH2 expression reflects a reaction to the inflammatory process in OLP necessitates additional research. [35]. In the study by Honarmand M et al. [36], salivary CRP (C-reactive protein) levels were

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considerably elevated in OSCC patients compared to those with OLP. Tvarijonaviciute et al. [37] reported that CRP also serves as a signal for poor prognosis in patients with OSCC. Ishikawa et al. [38] identified 15 substances that significantly differentiated between OSCC and OLP, as illustrated below, revealing the latent malignancy of OLP. Moreover, Lisa Cheng et al. [39] collected saliva samples from five groups and reported that IL-6 levels were markedly higher in OSCC patients than in active and inactive OLP patients. Shan et al. [40] reported that the salivary concentrations of solute carrier family 3 member 2 (SLC3A2) and S100 calcium-binding protein (S100 A2) were considerably higher in the OSCC group compared to both the healthy control group and the OPMD group. Furthermore, the salivary level of IL1RN (interleukin-1 receptor antagonist protein) was significantly reduced in the OSCC group compared to both the healthy control group ($p < 0.05$) and the OPMD group ($p < 0.05$).

Ghallab N A et al. [41] reported that the levels of the novel adipokines chemerin and matrix metalloproteinase-9 (MMP-9) were significantly greater in the serum and saliva of OSCC patients than in those of OPMD patients and control individuals. Mirzaii-Dizgah I et al. [42] reported that the mean salivary and serum levels of matrix metalloproteinase-3 (MMP-3) in OSCC patients were significantly greater than those in OLP patients. The concentration of MMP-3 rose from the reticular form of OLP to the erosive type, with further increases observed in both early-stage and late-stage OSCC. Similarly, Nosratzehi et al. [43] reported higher levels of MMP-2 and MMP-13 in patients with OSCC than in those with OLP and healthy individuals. Cheng Y S L et al. [44] found that the average salivary endothelin-1 (ET-1) level was significantly higher in patients with OSCC compared to those with active OLP lesions and patients in the remission phase of OLP. Totan et al. [45] reported that high expression of MMP-8 in OLP was associated with improved prognosis in tongue cancer patients.

Noted that the concentration of miRNA-27b was significantly higher in OSCC patients compared to healthy controls, individuals in remission from OSCC, and patients with OLP. Aghbari S M H et al. [47] reported the downregulation of miRNA-137, particularly in erosive OLP, suggesting that alterations in miRNA-137 gene expression could serve as biomarkers for disease activity and neoplastic tendency.

2.6 Oral lichenoid lesions (OLLs)

OLLs fundamentally represent an allergic reaction, with clinical and histopathological features indistinguishable from those of OLL, differing primarily in their predilection sites. OLL predominantly affects the buccal mucosa, lateral tongue borders or oral lips, presenting as solitary and localized lesions, whereas OLL commonly manifests bilaterally in the oral mucosa. Compared with OLLs, OLLs seem more prone to undergo malignant transformation. Cyclooxygenase-2 (COX-2) plays a crucial role as an enzyme in both inflammation and cell growth. The differences in the expression of COX-2 in different subtypes of OLD can distinguish a greater degree of precancerous lesions, and the overexpression of COX-2 also has potential for the prognosis of OLL and OLP [48].

2.7 Actinic cheilitis (AK/AC)

Actinic cheilitis (AC) most commonly affects the lower lip and is often mistaken by patients as a sign of aging, hence being overlooked until it reaches more advanced stages [49]. Twenty-seven percent of SCCs arise from AK lesions, and 56% of SCCs have AK lesions in close proximity. Souza L R et al. [50] reported that mast cells (MCs), eosinophils (ELs) and microvascular density (MVD) increased. The increase in MC and EL may be related to the stimulation of tumor angiogenesis. Moreover, the MVD can be used as an effective indicator for predicting cervical metastasis in patients with laryngeal SCC. This research group subsequently reported that changes in epithelial cells from precancerous lesions to malignant lip diseases and along with alterations in the levels of the p53, APE 1, hMSH2 and ERCC 1 proteins may contribute to the occurrence of lip cancer. When compared to the LSCC group, the immunoreactivity of p53 and APE 1 in the AC group was lower, and the expression of hMSH 2 and ERCC 1 was lower [51].

3. Discussion

Table 1 summarizes the differences in salivary biomarkers between various OPMDs and SCCs. Far from now, foundational studies focused mainly on biomarkers for OSCC. However, research regarding oral mucosal premalignant disorders (OMPDs) is relatively rare, often centering on specific biomarkers distinguishing OMPDs from healthy individuals rather than unique markers differentiating between OMPDs that have undergone malignant transformation and OSCC. In other oral premalignant

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conditions, such as OLE, congenital leukokeratosis, smoker's palate, and cGVHD , there is a significant gap in the detection of biomarkers. Focus should be on creating specific panels of salivary biomarkers that can not only differentiate between OPMDs and healthy tissue but also between OPMDs that have progressed to malignancy and established OSCC.

In OSCC patients, the concentrations of IL-6, 8 and TNF-α in saliva are markedly increased compared with those in OPMDs, suggesting their potential as broad indicators for diagnosing malignant transformation in OPMDs. However, these three markers are also associated with other conditions, such as psoriasis and breast cancer [52], necessitating the exclusion of other diseases when these indicators are utilized to refine diagnostic accuracy and reduce false positives.Meanwhile, further research into their specific cutoff values.

Exploration of the various genetic and epigenetic modifications associated with biomarker changes in saliva, which could provide insights into the underlying mechanisms of malignant transformation in oral tissues. Therefore, it further requires the development of implementation and testing of advanced diagnostic technologies such as digital microfluidics, nanotechnology, and biosensors to improve the detection sensitivity and specificity of salivary biomarkers. Meanwhile, these biomarkers still lack large-scale clinical trials to establish their clinical utility and reproducibility in diverse populations.

Table1 Differential salivary biomarkers for each Oral Potentially Malignant Disorder (OPMD) and Squamous Cell Carcinoma (SCC)

OPMD	Biomarkers	Indications in OSCC	Result	Ref
OL	SOD	Occurrence	Up	[4]
	IL-8	Occurrence	Up	[5][6][7][13]
	IL-6	Occurrence/prognosis	Up	[6][7]
	TNF-α	Occurrence/prognosis	Up	[7]
	HCC-1, PF-4	Occurrence	Up	[7]
	S1 P,Galactosylceramide, pseudouridine, 4-nitroquinoline 1-oxide, and inositol	Occurrence	Up	[8]
	IP 3R	Occurrence/prognosis	Up	[8]
	p-α Chlorophenylalanine, L-α Isoleucine, 4-α Fumaroyacetoacetate	Occurrence	Down	[8]
	KLK 5, uPA	Occurrence	Up	[9]
	GABA,Phenylalanine, Valine	Occurrence	Down	[10]
	Heneicosanoic Acid, Lactic Acid	Occurrence	Up	[10]
	SNCG	Occurrence	Up	[11]
	Plectin, LDHA	Occurrence	Up	[12]
	SA, OAZ, IL-1B	Occurrence	Up	[13]
	miRNA-21, 31	Occurrence/prognosis	Up	[14]
	hsa circ0001971, hsa circ0001874	Occurrence/prognosis	Up	[15]
	CD44 v6, CD44 v10	Occurrence	Up	[16]
	decanedioic acid, 2-methyloctacosane, eicosane, octane, 3,5-dimethyl,	Occurrence	Up	[17]

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	pentadecane, hentriacontane, 5, 5-diethylpentadecane, nonadecane, oxalic acid, 6-phenylundecanea, l-proline, 2-furancarboxamide, 2-isopropyl-5-methyl-1-heptanol, pentanoic acid, Docosane			
	Bacteroidetes	Occurrence	Up	[18]
	Fusobacteria	Occurrence	Down	[19]
PVL	TLR 2	Occurrence	Up	[19]
	Mcm-2, Mcm-5	Occurrence	Up	[20]
	P53, Ki-67	Occurrence	Up	[20][22]
	Geminin	Occurrence	Up	[22]
	Non-integral DNA	Occurrence	Up	[21]
	COX7B2, LINC00624, RCL1, HIST1H1C, NCLN	Occurrence	Up	[23]
	DKK 4, TMPRSSllB, SLC 6A 4, VSIG 2, SMPD 3, ABO, SLC 51 A, GALNT 5, GPX 3, DBNDD 1, TMEM 88 B, ZNF 215, SLC 46 A2, CLCN 1, KRT 3, NKX 2-β 3, BARX 2, ACAA 2, SLC 25 A42, PPAP 2B, HIBADH	Occurrence/prognosis	Down	[23]
	p16 INK 4a, p14 AR	Occurrence	Loss	[24]
OE	ALP, LDH	Occurrence	Up	[25]
	LDHA, ALDH2, PRDX1	Occurrence	Up	[26]
	HSPA1B, TXN	Occurrence	Down	[26]
OSMF	8-Isoprostane	Occurrence	Up	[27]
	LDHA	Occurrence	Up	[28]
	EGFR	Occurrence	Up	[29]
	RECEPTOR	Occurrence	Up	[30]
	IL-8	Occurrence	Up	[31]
	HIF-1α	Occurrence	Up	[32]
OLP	TNF-α	Occurrence	Up	[33]
	ALDH	Occurrence	Up	[34][35]
	CRP	Occurrence/prognosis	Up	[36][37]
	12 (trimethylamine N-oxide, putrescine, creatinine, 5-aminovalerate, pipecolate,	Occurrence	Up	[38]

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	N-acetylputrescine, gamma-butyrobetaine, indole-3-ac- etate, N1-acetylspermine, 2'-deoxyinosine, ethanolamine phosphate and N-acetylglucosamine			
	N-acetylhis- tidine and o-acetylcarnitine	Occurrence	Down	[38]
	IL-6	Occurrence	Up	[39]
	SLC3A2, S100 A2	Occurrence	Up	[40]
	Chemerin	Occurrence	Up	[41]
	MMP-9, MMP-3, MMP-2, MMP-13, MMP-8	Occurrence	Up	[41][42][43][45]
	ET-1	Occurrence	Up	[44]
	miRNA-27 b	Occurrence	Up	[46]
	miRNA 137	Occurrence	Down	[47]
OLL	COX-2	Occurrence/prognosis	Up	[48]
AK	MC, EL, MVD	Occurrence	Up	[50]
	p53, APE 1	Occurrence	Down	[51]
	hMSH 2, ERCC 1	Occurrence	Down	[51]

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